

(19)



Europäisches Patentamt

European Patent Office

Office européen des brevets



(11) Publication number:

0 448 762 A1

(12)

EUROPEAN PATENT APPLICATION

(21) Application number: 90106084.8

(51) Int. Cl.⁵: A61K 9/06, A61K 9/52

(22) Date of filing: 29.03.90

(43) Date of publication of application:
02.10.91 Bulletin 91/40

(84) Designated Contracting States:
AT BE CH DE DK FR GB IT LI NL SE

(71) Applicant: Kaufman, Herbert E.
300 Lake Marina Drive
New Orleans, Louisiana 70124(US)

(72) Inventor: Kaufman, Herbert E.
300 Lake Marina Drive
New Orleans, Louisiana 70124(US)

(74) Representative: Strehl, Schübel-Hopf,
Groening
Maximilianstrasse 54 Postfach 22 14 55
W-8000 München 22(DE)

(54) Ophthalmic treatment system.

(57) The invention provides an ophthalmic system which includes three-dimensional particles (10) of bioerodable material (12) suspended in a liquid carrier or ointment carrier (16) having a pH acceptable to the eye. The system provides (1) reliable, prolonged continuous administration of ophthalmic drugs (14) without irritating the eye, or (2) an artificial tear system which provides all of the components of the natural tear film layers, and thus when administered to the eye provides an effective tear film which mimics the natural tear film.

EP 0 448 762 A1

BEST AVAILABLE COPY

Most ocular treatments require frequent topical administration of drugs to the tissues of the ocular cavity. Further, in situations where there is a deficiency of tears or moisture in the eye, artificial tears must be applied frequently directly to the eye to provide moisture and lubrication.

For both situations, where additional lubrication and moisture are required in the eye, or where medication must be applied topically to the eye, one common form of treatment is the use of liquid drops. The liquid drop form is extremely easy to use as the patient merely self-administers the liquid through an eye dropper or dispenser which includes an eye drop extension end. However, a substantial disadvantage of the liquid form is that the medication or lubricating solution rapidly drains from the ocular cavity into the nasal cavity through an opening called the punctum. The draining liquid may be absorbed by the mucous membrane of the nose and throat causing systemic toxicity which could be minimized by using less drug and fewer administrations and holding the drug in more prolonged contact with the eye. Further, the liquid may simply evaporate from the eye.

Thus, with the use of liquid treatments, a continuous prolonged delivery of lubricant or medication is not achieved, and in the case of drug delivery, the exact dosage is unpredictable as the liquid drains out of the eye. Even with intermittent administration, the liquid treatment will continue to rapidly wash out of the eye, and the continued problem of unpredictability of dosage remains. Further, continuous administration of liquid is not only inconvenient, but may be dangerous.

Several systems shown in U.S. patents provide large ocular inserts to deliver drug to an eye continuously. Certain inserts disperse the drug and require removal of the carrier of the drug once the drug has been delivered. However, U.S. Patents 3,845,201; 4,164,559 and 4,179,497 show various inserts in the form of large pellets which dispense drug over a period of time and eventually are completely eroded, and thus do not require removal after drug delivery.

These inserts have certain advantages over the liquid treatments as more predictable dosage is obtained as there is a continuous dispensing of the drug over a period of time without rapid washout. Further, the inserts can be placed directly under the eyelid in the cul-de-sac of the conjunctival sac. Thus, the unitary ocular inserts provide predictable dosage over a period of time without the requirement of repeated applications as required with liquid treatments.

However, there are several disadvantages which accompany the use of unitary ocular inserts. First, as these inserts are fairly large, discomfort or irritation of the sensitive tissues of the eye may

occur. Further, the unitary inserts must be carefully placed under the eyelid, and require special care and special insert devices for insertion. Difficulties in patient education in inserting these inserts and compliance with proper technique have prevented their widespread use. Also, as the ocular inserts are rather large and unitary, they are sometimes accidentally ejected from the ocular cavity by the blinking action of the eyelids.

In an attempt to address the problems of liquid treatments and ocular inserts, U.S. Patents 3,914,402; 4,001,388 and 4,115,554 all to Shell, show ophthalmic forms which include a suspension of solid particles from 10 to 300 microns in largest dimension in a liquid medium. The Shell dosage form alleviates certain problems associated with ocular inserts, such as complicated insertion, discomfort due to size and the possibility of the insert popping out. However, due to the extremely small size of the solid particles in the suspension of Shell, an extremely important advantage of the ocular inserts is lost, namely the predictability of dosage and continuous dispensing of drug or lubricant.

In all of the Shell patents, it is specifically stated that the solid particles of the suspension are small enough to be passed from the ocular cavity through the punctum. Further, this is evident from the range of the particle size as being from 10 to 300 microns in largest dimension, and the average size of the punctum is about 0.5mm. Thus, Shell intentionally provides solid particles smaller than the punctum. Shell asserts that the particles of the suspension do not drain from the ocular cavity through the punctum. Although Shell makes this assertion, in practice it cannot be explained why particles smaller in diameter than the punctum would not wash and drain out of the eye in the normal course of drainage provided by the duct system. Further, as the particles in Shell are delivered in a liquid suspension, the excess liquid delivered to the eye would naturally drain through the punctum. As the particles are suspended in this liquid and are specifically smaller than the punctum diameter, it cannot be seen what would prevent the particles from draining out of the eye when delivered with the draining liquid. Thus, although Shell asserts otherwise, the tiny particles in the Shell suspension would not provide a predictable dosage as some of the particles would have to wash out through the punctum with the excess liquid delivered with the Shell system. Although some of the particles in Shell may actually lodge in the soft tissues of the eye, a substantial number of particles will drain out of the eye.

U.S. Patent 3,826,258 to Abraham shows a gradual release medicine carrier. Abraham addresses topical treatment of the eye using capsules

which are dropped into the eye. Abraham addresses the problem of irritation or discomfort in the eye by broadly stating that the diameter of the spherical capsules should be less than about 1 millimeter. Abraham does not address a specific size which would not cause irritation in the eye and broadly states a maximum diameter. However, a maximum diameter of about 1 millimeter would be very irritable to the eye.

Further, Abraham does not address the problem of particles draining through the punctum of the eye. Abraham does not suggest a minimum dimension of the capsules to prevent drainage through the punctum. The punctum has an average size of 0.5 millimeters and thus, a large portion of Abraham's broad size range of capsules would drain through the punctum. Abraham in no way addresses the problems of drainage through the punctum and broadly states that the capsule should not be irritable to the eye without really giving any further guidance, of dimensions or consistency which would achieve this single broadly recited purpose related to size.

Further, Abraham in no way discusses balancing of the smallest dimension as opposed to a largest dimension such that concerns of irritation as well as drainage through the punctum are both accounted for. On the contrary, Abraham suggests the use of spherical capsules which presumably would have uniform dimensions. Thus, there is no suggestion in the Abraham patent to create dimensions of the capsule in order to help prevent drainage through the punctum without increasing the possibility of irritation to the eye.

Thus, an object of the present invention is to provide an eye treatment system and method of treatment which provides a continuous administration of the treatment media over a period of time.

It is a further object to provide a treatment system method which delivers a predictable dosage or amount of treatment media to the eye. It is a further object to provide an ophthalmic treatment system easily administered to the eye which will remain in the ocular cavity over a period of time without the risk of premature drainage or popping out of the eye.

It is a further object to provide an ophthalmic treatment system that is prolonged because drainage from the eye through the punctum is prevented, delayed or hindered, and which at the same time is comfortable such that it does not irritate the sensitive eye tissue.

The present invention retains all the advantages of the known treatment systems discussed above, while obviating all of the disadvantages associated therewith.

These and other objects are achieved by providing an ophthalmic treatment system which in-

cludes three dimensional particles of bioerodible material being at least 0.5 mm in greatest dimension and being no greater than about 0.4 mm to 0.7 mm in smallest dimension when disposed in the ocular environment. These particles are suspended in a liquid carrier or ointment carrier having a pH acceptable to the eye. In this treatment system, the bioerodible material is released in the eye as the particles erode in response to the ocular environment. Methods for treating the eye are also provided using the system discussed above.

Due to the specific minimum size of the largest particle dimension, the present invention provides optimum prevention of drainage through the punctum, and thus provides optimum prolonged delivery, as well as a predictable dosage that will remain in the eye. It should be noted that this specification is merely a minimum, and it is contemplated that the largest dimension be 4 mm or even greater to maximize the amount of material delivered. At the same time, due to the specific size of the smallest particle dimension in the ocular environment, the treatment system will not be uncomfortable or irritate the eye.

The present invention thus includes the advantages of prior suspensions of particles no greater than 300 microns, as well as liquid treatments in ease of application, no risk in being dislodged from the eye once applied, and minimal irritation or discomfort. However, the present invention also avoids problems associated with prior liquid treatments and suspensions of minute particles which are smaller in size than the punctum, such as the drainage of the treatment in these systems out of the eye through the punctum when applied to the eye.

Further, the present invention includes the advantages of solid inserts such as predictable dosage, and prolonged release of the treatment without drainage through the punctum. However, the present invention also avoids problems associated with solid inserts such as discomfort or irritation of the eye, blurred vision, complicated insertion requiring special skills and equipment, and the risk of being ejected from the eye during blinking.

According to other advantageous features of certain preferred embodiments of the invention, drug is provided in the particles of bioerodible material. Thus, the suspension provides a drug delivery system to the ocular environment.

According to other advantageous features of certain preferred embodiments of the invention, the system serves as an artificial tear treatment. According to certain of these embodiments, the bioerodible material itself provides the artificial tear treatment to the eye when eroded by the ocular environment. Such a system provides proper lubrication and wetting. In certain preferred embodi-

ments, other natural components of the tears are included in the particles or in the solution. Specifically, in certain embodiments, lipid is included in the particles or in the solution.

When employed as an artificial tear system, the system can be used for various treatments including the treatment of dry eye syndrome, whenever lubrication of the eye is desirable or when the eyes are subjected to dry conditions.

Under normal conditions, ocular fluid forms a thin layer approximately 7-10 m thick that covers the corneal and conjunctival epithelium. This ultra thin layer provides a smooth optical surface to the cornea by abolishing minute surface irregularities of its epithelium, wets the surface of the corneal and conjunctival epithelium, thereby preventing damage to the epithelial cells, and inhibits the growth of microorganisms on the conjunctiva in the cornea by mechanical flushing.

The tear film normally includes a three layer structure. The outermost layer is a lipid layer derived from the secretions of the meibomian glands and thought to retard evaporation of the aqueous layer. The middle aqueous layer is provided by the major and minor lacrimal glands, and contains water-soluble substances. The inner most mucinous layer is composed of glycoprotein mucin and overlies the corneal and conjunctival epithelial cells. The epithelial cell membranes are composed of lipoproteins and are thus generally hydrophobic. The mucin plays an important role in wetting the surface, as the aqueous solution alone cannot wet this surface. Thus, the mucin provides a hydrophilic surface for the aqueous tears to spread out on and the surface is wetted by a lowering of the tears' surface tension. Under normal conditions, mucin is provided by goblet cells of the conjunctiva and is also provided from the lacrimal gland.

When any of the tear film components is deficient, the tear film will break up, and dry spots will form on the corneal and the conjunctival epithelium. Deficiency of any of the three components (aqueous, mucin or lipid) may result in dryness of the eye. There are many forms of the disease known as keratoconjunctivitis sica. Those connected with rheumatoid arthritis or other connective tissue disease are referred to as Sjögren's syndrome. All of this background information is discussed in the chapter on tears by Tabbara in Vaughan et al., General Ophthalmology, 11th Ed. (1986), pp. 72-77.

It is known to provide a large, solid, artificial tear insert which is placed into the eye. An example of such an insert is sold under the trademark LACRISERT. This rod contains hydroxypropyl cellulose which is slowly released over a period of time in the ocular environment. It is also suggested in Chapter 7 of General Ophthalmology to also

apply topical artificial tears to the eye once the inserts are in place.

Not only do these large inserts sometimes cause irritation or blurring of vision, the inserts provide but one material which mimics only one layer of the tear film. The hydroxypropyl cellulose provides the mucin-type material to the tear film. Further, this treatment is not provided in an easy to use suspension form which delivers all of the treatment simultaneously to the eye. The insert must be placed in the eye using special techniques and then artificial tears could be added. The General Ophthalmology book does not discuss the actual composition of the artificial tears which may be added once the solid insert is in place.

As dry eye syndrome can be caused by deficiency of any of the three tear film components, the LACRISERT system does not provide a complete treatment for all cases of dry eye syndrome as all three components of the tear film layers are not present in the LACRISERT system.

It is thus an object of the present invention to provide an artificial tear treatment system which provides all components of the tear film layers. It is a further object to provide a treatment system to treat dryness of the eye successfully by providing all components which will form a tear film mimicking the natural tear film when administered to the eye. Thus, an object is to provide an artificial tear system which compensates for the deficiency of any or all of the natural tear film components, namely aqueous, mucin or lipid.

It is a further object to provide an artificial tear system which can be used any time lubrication is required for the eye or any time the eye is subjected to dryness. Thus, it is an object to provide an artificial tear system which can be used as ophthalmic lubricants, contact lens solutions, gonioscopic lens solutions, and other artificial tear systems.

Further objects include providing an artificial tear system which is easy to administer and which provides an effective delivery of the three components of the tear film.

These objects and other objects are achieved by providing an artificial tear suspension system. The system includes bioerodible mucin-type particles which release mucin-type material when placed in an ocular environment. Lipid-type material is provided which releases lipid-type material when placed in the ocular environment. Further, aqueous-type material is provided which releases aqueous-type material when placed in the ocular environment. The mucin-type particles are suspended in either the lipid-type material or the aqueous-type material or both.

The present invention provides an easy to administer system with effective delivery of all three

of the components of the tear film layers. Once administered to the eye, the present invention three component system provides a tear film which perfectly mimics the natural tear film. Further, if natural production of any of the three components of the tear film is deficient, the present system compensates therefore, and thus is a very effective treatment of dryness of the eye, regardless of the cause.

According to other advantageous features of certain preferred embodiments of the invention, the particles are in a soft, malleable form such that the particles are deformed by the eyelid when placed in the ocular environment between the eyelid and the eye, and are not irritating to the eye if disposed between eyelids. In further preferred embodiments, the particles can be in a semi-solid form and thus are malleable and provide comfort to the eye. In certain embodiments, the size of the smallest dimension is greater than the preferred range prior to administration, and are compressed to the preferred range when administered to the eye. The malleable form or consistency provides a soft contact to the eye tissue and forms rounded edges, thereby further enhancing comfort.

Methods of treatment corresponding to the various preferred embodiments are also provided.

Other objects, advantages and novel features of the present invention will become apparent from the following detailed description of the invention when considered in conjunction with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a magnified view of the particles of bioerodible material according to certain embodiments of the present invention;

Figure 2 is a magnified view of particles of the bioerodible material according to other advantageous embodiments of the present invention; and

Figure 3 is a pictorial view showing administration of the ophthalmic treatment system into the conjunctival sac of the eye.

DETAILED DESCRIPTION OF THE DRAWINGS

In its simplest form, the present eye treatment system includes three-dimensional particles of bioerodible material of a specific size as will be discussed below, which are suspended in a liquid carrier or ointment carrier having a pH acceptable to the eye. The liquid medium employed in the present suspension system may be an aqueous or non-aqueous ophthalmically acceptable sterile liquid. Suitable non-aqueous liquid media include the physiologically acceptable oils such as silicon oil, USP mineral oil, white oil, and vegetable oils, for example, corn oil, peanut oil or the like.

To achieve a uniform dispersion of the particles in the liquid, the density of the liquid medium can be chosen such that it is equal to the density of the particles. Therefore, the particles will not float to the top of the liquid or sink to the bottom. If the liquid medium does not have the same density of the particles, the viscosity of the liquid medium can be adjusted in order to provide a uniform dispersion, or the dispensing system can achieve a dispersion by shaking or proper mixing immediately before administration.

In certain embodiments, the eye treatment liquid medium contains a variety of other materials to adjust pH, render the medium isotonic, preserve the treatment system and the like. Preservative agents which can be used include benzalkonium chloride in a concentration range of from 1:15,000 to 1:30,000; chlorobutanol in a concentration range of from 0.3% to 0.8%; thimerosal in a concentration range of from 0.001% to 0.003%; and phenyl mercuric nitrate in a concentration range of from 1:60,000 to 1:80,000. Also, in certain preferred embodiments, unpreserved unit or daily dose systems can be used. Other agents may be added to increase viscosity, promote suspension and/or improve ocular compatibility, such as methyl cellulose in an amount of from 0.1% to 0.7% or poly (vinyl alcohol) in an amount of from 0.4% to 2.0%. These and other additive materials are known in the art. A variety of these materials is generally described in the book Contact Lens Practice, Robert B. Mandell (Charles C. Thomas, 1965) at pp. 159-165, which description is herein incorporated by reference.

In certain preferred embodiments, instead of using a liquid medium for the suspension, the particles can be suspended in an ointment such as lanolin, petrolatum and other known ointments.

The particles suspended in the liquid or ointment medium should be made of material which is bioerodible such that removal of the particles from the eye is not required as they are broken down and absorbed in the ocular environment (or resorbed). The term "bioerodible" is defined as a material which innocuously disintegrates or breaks down from a unit structure or enclosure over a prolonged period of time in response to the environment of the eye by one or more physical or chemical degradative processes, for example, enzymatic action, hydrolysis, ion exchange, dissolution by solubilization, emulsion formation or micelle formation. The bioerosion of the particles not only prevents a build-up of particles in the tissues of the ocular cavity, but also provides prolonged release of the treatment in the eye which can be controlled such that the treatment is predictable.

Bioerodible materials used in the particles of the present suspension of this invention should be non-toxic and compatible with any drug which may

be delivered therewith. In certain preferred embodiments, the bioerodible materials should be capable of absorbing drugs in which they are soaked, and in certain other preferred embodiments, the bioerodible materials should be capable of forming films which wholly surround and enclose a drug or other active agent to be delivered to the eye.

The particles should be comfortable when they are under the eyelids, as well as when they are on the surface of the eye in between the eyelids in the interpalpebral area, for example. In certain preferred embodiments, the particles are soft to help assure this comfort.

There are several naturally occurring materials, as well as synthetic materials, which are biodegradable and suitable for the present invention.

Examples of synthetic polymers that can be prepared which are biodegradable include polylactides and polyglycolic acid. These biodegradable polymers are broken down into innocuous products such as carbon dioxide and water and they are also commercially available.

Useful polylactides includes both homopolymers and copolymers. Usually, these polylactides are prepared from the cyclic esters of lactic acids. Both L(+) and D(-) forms of lactic acid may be used to prepare the polylactides as well as the optically inactive DL-lactic acid mixture or any desired mixtures of D(-) and L(+) lactic acids.

Lactide copolymers offer an important degree of flexibility in choosing the life of a polymer matrix since this can be controlled through the amount and type of comonomer used. Some illustrative examples of suitable comonomers include: glycolide, -propiolactone, tetramethylglycolide, -butyrolactone, gamma-butyrolactone, pivalolactone, and intermolecular cyclic esters of -hydroxybutyric acid, -hydroxyisobutyric acid, -hydroxyvaleric acid, -hydroxyisovaleric acid, -hydroxycaproic acid, -hydroxy- ϵ -ethylbutyric acid, -hydroxyisocaproic acid, -hydroxy- γ -methylvaleric acid, -hydroxyheptanoic acid, -hydroxyoctanoic acid, -hydroxydecanoic acid, -hydroxymyristic acid, -hydroxystearic acid, -hydroxylignocenic acid, and phenyllactic acid.

Methods of preparing polylactides are well documented in the patent literature. The following U.S. Patents, the teachings of which are hereby incorporated by reference, describe in detail suitable polylactides, their properties and their preparation: Dorough, 1,995,970; Schneider, 2,703,316; Salzberg, 2,758,987; Zelle, 2,951,828; Higgins, 2,676,945 and 2,683,136; Trehu, 3,531,561; British Patent Specifications 755,447; 799,291; 825,335; 901,037; 932,382; 1,048,088; 1,123,445; West German Patents 946,664; 975,191; 1,112,293; 1,152,258; 1,153,902; East German Patent 14,548; French Patents 1,425,333; 1,478,694; 1,512,182;

Netherlands Patent 99,836; Netherlands Patent Applications 6,605,197; 6,605,292; Japanese Numbers 17,675 (1966); 7,796 (1967); 2,948 (1968); 15,763 (1969).

Polyglycolic acids have recently been found to possess excellent biodegradable properties. Polyglycolic acid is the homopolymer of glycolic acid (hydroxyacetic acid). In the conversion of glycolic acid to polyglycolic acid, glycolic acid is initially reacted with itself to form the cyclic ester glycolide, which in the presence of heat and a catalyst is converted to a high molecular weight linear-chain polymer. Polyglycolic acids and their properties are described in more detail in the following article, the teachings of which are hereby incorporated by reference: "Cyanamid Research Develops World's First Synthetic Absorbable Suture", Chemistry and Industry, July 11, 1970, page 905.

The molecular weights of polypeptides and polyglycolic acid are closely related to both the exudation of the drug and the biodegradation of the matrix. It has been found that high molecular weights, i.e., $M_w = 90,000$ or higher result in polymer matrices which retain their structural integrity for longer periods of time, while lower molecular weights, i.e., $M_w = 30,000$ or below, result in both slower exudation and shorter matrix lives.

A preferred particle material is collagen such as that obtained from pig sclera or cow skin and cross-linked with ultraviolet, or other forms of collagen cross-linked either by ultraviolet or X-ray.

The chemistry of a molecular structure and biochemical properties of collagen have been well established. The use of collagen as a vehicle for drug delivery as a bio-material is well known. U.S. Patent 1,464,559 to Miyata et al. lists several publications discussing the use of collagen in drug delivery. An example is "Annual Review of Biophysics and Bioengineering", Vol. 3, pp. 231-253, 1974, by Miyata et al. Another example is Rubin et al., J. Clin. Pharmacol., Vol. 13 (8/9):309-312 (1973), "Collagen as a Vehicle for Drug Delivery".

Collagen is a major protein of connective tissue such as cornea, skin, etc., and can be solubilized and purified by the treatment with proteolytic enzymes (other than collagenase) such as pepsin. Solubilized collagen is telopeptides-poor, relatively inexpensive, not antigenic and useful as a biomedical material. Enzyme solubilized native collagen is soluble in acidic pH, and soluble at physiological pH and at body temperature.

Native collagen is insoluble at physiological pH and at body temperature. Thus, native collagen must be changed such that the collagen erodes in the ocular environment so that physical removal thereof is not required.

The U.S. Patent to Miyata et al. shows various forms of chemically modified collagen which is

erodable in the eye under physiological pH and under normal body temperatures.

Another material which can be used for the particles of the present invention is gelatin which is obtained by the selective hydrolysis of collagen and includes a complex mixture of high molecular weight water soluble proteins.

As used herein, the term cross-linked gelatin means the reaction product of gelatin or a gelatin derivative with a cross-linking agent which is reactive with either the hydroxyl, carboxyl or amino functional groups of the gelatin molecule but is substantially unreactive with the peptide linkages of the gelatin molecule. The product of cross-linking reaction preferably has an average molecular weight of from 20 to 50,000 between cross-links, while higher values can also be employed. These reaction products bioerode in the environment of the eye over a prolonged period of time.

Cross-linked gelatin materials and their preparations are well known. The degree of gelatin cross-linking is dependent upon the processing conditions employed and markedly affects the gelatin's bioerodability. Exemplary cross-linking agents are: aldehydes, such as monoaldehydes, e.g., C₁-C₄ aldehydes, dialdehydes, epoxides, para-benzene quinone, and aqueous peroxydisulfate.

Aldehydes and ketones, especially the 1 to 4 carbon aldehydes and ketones are preferred, with formaldehyde being a most preferred cross-linking agent.

Irradiation is another suitable method for cross-linking gelatin; see for example Y. Tomoda and M. Tsuda, J. Poly Sci., 54,321 (1961).

The reactive hydroxyl, carboxyl and amino groups are respectively present in gelatin in the appropriate amounts of 100, 75 and 50 meq per 100 grams. These quantities may serve as a general guide in determining the amount of cross-linking agent to be used.

Cross-linked gelatin is relatively permeable to ocular fluid so that diffusion of drug through gelatin may take place to some extent. Thus, cross-linked gelatin is a good example of a release rate-controlling material which releases drug by a diffusion mechanism.

Other materials which can be used for the particles include polymers of polyvinyl alcohol, methyl cellulose, carboxy methyl cellulose, hydroxypropy methylcellulose and lipids, which may include lecithin, cholesterol, fatty alcohols and other related materials. Particles can also include methyl cellulose derivatives and can include a combination of the bioerodible materials discussed above. Further, treatment system can include a variety of different types of particles having different components to thereby vary the rate of erosion. Further,

certain bioerodible materials may be more advantageous for absorbing and releasing certain active agents to be delivered to the eye.

Crystallinity also affects the exudation and biodegradability rates. The polymer matrices having higher degrees of crystallinity have slower exudation rates and slower biodegradability. It is known that the crystallinity has a marked effect on physical properties. See Flory, Paul J., Principles of Polymer Chemistry, 5th printing, 1966 at pp. 49 et seq. It has also been reported in the literature that gaseous diffusion through polymeric membranes is slower, in general, for those polymers having higher degrees of crystallinity. See Michaels, A. S. and Bixler, H. J., "Flow of Gases through Polyethylene and Rubbery Polymers," J. Poly. Sci., vol. 50, pp. 413-439 (1961).

A good amount of control over the release of drug can be obtained by choosing appropriate molecular weights and degrees of crystallinity in the polymer matrix. For example, if a relatively long release duration is desired, a high molecular weight polymer formed from a pure optical isomer of lactic acid can be used for the matrix; on the other hand, if a rapid release rate is desirable over a short duration, a low molecular weight lactide copolymer having a lower degree of crystallinity can be synthesized for use as the polymer matrix. Those skilled in the art will know or be able to determine by routine experimentation many suitable combinations of molecular weights and degrees of crystallinities of polylactides or polyglycolic acid to accomplish a desired release rate and duration.

Using one or more of the above parameters, polymeric matrices can be designed which have a great variety of exudation rates and biodegradability. Matrices can be synthesized to have lives shorter than, equal to or longer than the period of effective drug delivery. For the shorter matrix lives, drug delivery will be accomplished by a combination of drug exudation and matrix biodegradation; for the longer matrix lives, drug delivery will be substantially dependent on only drug exudation. The degree of flexibility thus offered in designing drug dispensing system of this invention is of great significance.

Further, the particles of the present invention, according to certain preferred embodiments, should be soft and malleable such that pressure created by the eyelid and the eye will deform the particles. In certain preferred embodiments, the particles can actually be in a semi-solid form as long as the particles do not dissolve in the liquid or oil medium in which they are suspended before administration to the eye.

Preferred methods for forming semi-solid particles include hydrating substances such as gelatin, collagen or polymers immediately before insertion

or placing soft hydrated solids in a mixture or ointment base that will not permit them to dehydrate.

Hydration is generally performed by exposure of the particles to an aqueous solution such that water is incorporated into the particles. The particles should remain hydrated when administered to the patient.

The bioerodible material particles can be hydrated by placing the material in the aqueous solution carrier discussed above. The aqueous carriers will hydrate the particles, and if the particles are left in the carrier, dehydration will be prevented.

Also, the bioerodible material can be hydrated by placing it in a drug soaking solution. Dehydration is prevented by placing the drug soaked particles in the aqueous carrier or in an ointment carrier. When dispersed in the ointment, the water will be retained in the particles and dehydration will thus be prevented by the ointment carrier.

When lipid is used as the bioerodible particle material, hydration is not necessary as lipid is already in a soft, malleable form.

Other methods for making materials which can be used for the particles of the invention malleable in form are known.

Although plasticizers are not the most preferred means to provide soft, malleable particles, examples of plasticizers which can be used in the present invention are shown in U.S. Patent 4,179,497 to Cohen et al which shows large bioerodible inserts. A requirement of any plasticizers used is that the material be completely soluble in the ocular environment. Examples of suitable plasticizers include water, polyethylene glycol, propylene glycol, glycerine, trimethylol, propane, di and tripropylene glycol, hydroxypropyl sucrose and the like. Plasticizers can be present in the particles in various ranges. Although not the most preferred method of providing softness and malleability when plasticizers are used, they should be used in the lowest concentration possible and not greater than 20%.

Cohen et al recites a method of plasticizing a solid insert product with water. As applied to the present invention, the particles are contacted with air, having a relative humidity of at least about 40% until the particles pick up at least about 5% water, thereby becoming softer and more pliable. In certain preferred embodiments, the relevant humidity of the air is from about 60% to about 99% and the contact is continued until the water is present in the particles in amounts of from about 10% to about 20%.

Any bioerodible material which is compatible with any drug dispersed therein, is non-toxic, has the desired encapsulation properties or properties for dispersion of drug throughout, and has appro-

priate diffusion and erosion properties might also be used. The materials discussed above are examples of preferred embodiments, but should in no way limit the materials used for the particles of the present suspension.

According to certain preferred embodiments, the particles of bioerodible material include drugs incorporated therein. The drugs can be either dispersed throughout the bioerodible material or encapsulated by the bioerodible material. The term "drug" is used in this description in its broadest sense, and covers all drugs used in any mammal. Drugs which are useful in the ocular area are specifically desired, although the present invention is not limited to only ocular drugs. The term "drug" is defined in the present invention as including, but not limited to the following classes of drugs: therapeutic drugs, preventative drugs, diagnostic drugs and any other drugs. It is to be understood that a variety of classes, subclasses and specific examples of drugs not expressly mentioned herein are within the scope of this invention and other examples of drugs are well known and are easily ascertainable to those skilled in the art.

Drugs suitable for incorporation in the particles of the suspension, consistent with their known dosages and uses, are without limitation ophthalmic drugs including: antibiotics such as tetracycline, chlortetracycline, bacitracin, neomycin, polymyxin, gramicidin, oxytetracycline, chloramphenicol, gentamycin, penicillin, kanamycin, amikacin, sisomicin, tobramycin, garamycin, ciprofloxacin, norfloxacin and erythromycin; antibacterials such as sulfonamides, sulfacetamide, sulfamethizole and sulfisoxazole; antivirals, including idoxuridine; and other antibacterial agents such as nitrofurazone and sodium propionate; anti-allergens such as antazoline, methapyriline, chlorpheniramine, pyrilamine and prophenpyridamine; anti-inflammatories such as cortisone, hydrocortisone, hydrocortisone acetate, dexamethasone, dexamethasone 21-phosphate, fluocinolone, medrysone, prednisolone, methylprednisolone, prednisolone 21-phosphate, prednisolone acetate, fluorometholone, betamethasone, fluocortolone, indomethacin and triamcinolone; decongestants such as phenylephrine, naphazoline and tetrahydrazoline; miotics and anticholinesterases such as pilocarpine, eserine salicylate, carbachol, di-isopropyl fluorophosphate, phosholine iodide, echothiophate, physostigmine and demecarium bromide; mydriatics such as atropine sulfate, cyclopentolate, homotropine, scopolamine, tropicamide, eucatropine, and hydroxyamphetamine; sympathomimetics such as epinephrine and immunosuppressants such as cyclosporin and azathioprine.

In its embodiments as an artificial tear system,

the present invention provides a system which in simplest form includes bioerodible mucin-type material particles, a lipid-type material and an aqueous-type material. The particles are suspended in the lipid-type material or the aqueous-type material which serves as a carrier. Thus, the material of all three layers is provided in one easy to administer suspension.

It is contemplated that in certain particularly preferred embodiments, the particles of bioerodible material also include various other components of natural tears in addition to or without components of the natural tear film layers as discussed above. The additional tear component material is either dispersed throughout the bioerodible particle, is encapsulated by the bioerodible material, or is included in the liquid or ointment carrier. Thus, according to certain preferred embodiments, other materials which can be included in the artificial tear bioerodible particles are glycoprotein mucin, lipoproteins, proteins such as albumen, globulins and lysozyme glucose, tear urea and other components such as those which assure a proper pH for the ocular environment.

According to other advantageous embodiments, topical solutions which have been used in eye drop form as artificial tears can be encapsulated in the bioerodible particle such that as the outer coating erodes, the artificial tears can be released to the eye over a period of time.

The mucin-type material should mimic the mucin component layer of the tear film. Thus, the material should act to hold aqueous material on the corneal and conjunctival epithelial cells. As discussed above, the epithelial cell membranes are composed of lipoproteins and are therefore relatively hydrophobic, and thus the surface cannot be wetted with an aqueous solution alone. Mucin plays the important role of wetting the surface. The mucin is partly adsorbed onto the corneal epithelial cell membranes and is anchored by the microvilli of the surface epithelial cells. This provides a new hydrophilic surface for the aqueous tears to spread on, and the surface is wetted by a lowering of the tears' surface tension.

Thus, the mucin-type material provided in the present system should hold aqueous material to the surface of the epithelial cells. This aqueous material can be the natural tear fluid or the aqueous material provided in the present system. Thus, the mucin-type material particles bind aqueous material on the eye much like the natural mucin component of the tear film.

The several biodegradable, naturally-occurring and synthetic materials discussed above are suitable for the mucin-type material of the present invention.

For the tear system preferred methods for for-

ming semi-solid particles include hydrating substances such as gelatin, collagen or polymers immediately before insertion or placing soft hydrated solids in a mixture or ointment base that will not permit them to dehydrate. Not only does the hydration provide soft, malleable particles, but also the water incorporated into the particles during hydration is delivered in the system as at least part of the aqueous component. Once in the eye, the mucin-type material particles mimic the natural mucin and hold and bind the water to the eye. Thus, the hydrated particles provide aqueous material in addition to the aqueous material when water is used as the liquid carrier. Further, when hydrated particles are placed in a lipid-type ointment or oil carrier, the ointment or oil forces the water to remain in the particles as the ointment or oil medium is hydrophobic. Thus, in ointment or oil medium, the present invention can provide the aqueous component of the tear film from the water incorporated into the hydrated particles.

Hydration is generally performed by exposure of the particles to an aqueous solution such that water is incorporated into the particles. The particles should remain hydrated when administered to the patient.

The bioerodible material particles can be hydrated by placing the material in an aqueous solution carrier as discussed above. The aqueous carriers will hydrate the particles, and if the particles are left in the carrier, dehydration will be prevented.

Also, the bioerodible material can be hydrated by placing it in an aqueous soaking solution. Dehydration is prevented by placing the drug soaked particles in an aqueous carrier or in an ointment carrier. When dispersed in the ointment, the water will be retained in the particles and dehydration will thus be prevented by the ointment carrier.

The lipid-type material can be provided in particle form and/or in the form of a liquid or ointment carrier for the mucin-type material particles. The lipid-type material can include all of the known lipids such as phospholipids, glycolipids and cholesterol. Further, the lipid can be in the form of waxes, esters, lecithin, fatty alcohols and fatty acids. Also, the lipid can be in the form of petrolatum, either as an ointment carrier or as suspended particle globules. The term "particle" as defined herein encompasses globules or semi-solid masses. When suspended in an aqueous carrier, the lipid can also be in the form of micelles, liposomes, a bilayer, a globule or any other form. Further, the carrier medium can be a two component medium including both lipid-type materials, such as oil, and aqueous material. Such a system should be well shaken immediately prior to administration to assure mixing of the two carrier components.

The function of the lipid layer of the tear film provides a smooth surface and is thought to retard evaporation of the aqueous layer. Any material which is non-toxic and achieves these purposes can be used as the lipid-type material. The lipid-type material provides a monolayer or continuous aqueous surface versus a discontinuous layer.

When the lipid is placed in the ocular environment, it is broken down by enzymes in the ocular environment such as by hydrolyzation or is melted by the body temperature present in the ocular environment, for example. Thus, if the lipid-type material is in a particle or semi-solid particle form suspended in the carrier, the lipid particles will not dissolve, but when placed in the ocular environment, the lipid particles will dissolve and provide lipid material for the lipid layer of the tear film.

Thus, the artificial tear system according to the present invention provides equivalents of all three components of the natural tear film in an easy to administer suspension. There are several combinations of the form of each of the three components in the suspension system which are contemplated. The present invention should not be limited to any specific form or combination of forms. The carrier can provide the aqueous component and/or the lipid component. Similarly, particles of the present suspension can provide any combination of the mucin component, the lipid component and the aqueous component. According to other advantageous embodiments, the artificial tear particles can be suspended in an oily or other lipid vehicle medium.

There are several processes which can be used to form the bioerodible particles of the present invention.

One method includes using a liquid or a mixture of the bioerodible material which is poured onto a flat surface. The film created is then allowed to dry as the solvent evaporates. Once the film has dried, the individual particles can be cut using known methods. A variety of methods can be used to cut the film into individual particles. According to most embodiments, this cutting can be done by a preformed mold cutter having the proper dimensions.

The film should generally have a thickness of no greater than 0.5 mm if this thickness is to be the smallest dimension of the particles. This thickness can be assured by preparing the proper fluid phase of the bioerodible material. As an example, a solution of gelatin, collagen or carboxy methyl cellulose, for example, can be dried and then cut to the specific shape and dimensions or allowed to dry in appropriate molds.

According to certain preferred embodiments, the liquid mixture of bioerodible material is poured into a shallow pan or half-mold to the desired

thickness. In certain embodiments, the pan or mold can include markings around the sides to indicate the thickness poured. In this way, the proper thickness can be assured. Subsequent to drying the particles are then cut in the remaining two dimensions.

In certain embodiments the liquid phase of the bioerodible material is not hydrated (the solvent is not aqueous). Further, even if the liquid phase is hydrated during pouring, the film or mold-forms are subsequently dehydrated when dried. In certain embodiments, the film or cut particles should be subsequently hydrated by soaking in an aqueous solution. The hydrated film or particles will expand to a certain degree depending on the amount of water incorporated therein. Thus, when determining the thickness of the film of bioerodible material which is not hydrated, the expected increase of thickness due to hydration should be compensated for by pouring a thinner film. However, due to the hydration, the particles will be soft and malleable in form. Therefore, the particles can be thicker than the preferred range of 0.4 mm to 0.7 mm, as the particles will compress to the desired range when subjected to forces between the eyelid and the eye. Also, as the particles are soft, they should conform to the eye and be comfortable even when disposed between the upper and lower eyelids.

In certain preferred embodiments, the preferred hydrated thickness (smallest dimension) is in the range of about 0.5 - 0.75 mm. However, if malleable, especially if semi-solid in form, the smallest dimension can be up to 1 mm if administered to the eye between the eyelid and the eye where pressure will compress the particles to the proper thickness.

Pouring of the film is but one method of controlling the thickness. Other methods include pouring into molds of the proper dimension, and cutting dried masses of the material to the proper thickness. The method of forming the particular thickness should not be limited to the examples given above. Regardless of the method for forming the proper dimensions, the preferred ranges of dimensions are discussed below.

The smallest dimension of the three-dimensional particles should have a thickness of no greater than about 0.4 mm to 0.7 mm when placed in the ocular environment. Depending upon the composition of the particles, if compression of the particles is not expected in the ocular environment, the particles should be either cut to this specific smallest dimension, or have a film thickness of this dimension. However, in preferred embodiments, the bioerodible particles are made such that they are malleable, and thus can be cut to a size larger than the given range of the smallest dimension, as long as the particles will be deformed and com-

pressed to the proper size range by the pressure between the eyelid and the eye. These methods of making the particles malleable are discussed above. Although the exact dimensions vary according to the specific materials and degree of deformation associated therewith, according to certain preferred embodiments, the particles that will be compressed should be cut such that the smallest dimension is no greater than 0.4 mm to 1.0 mm prior to administration to the eye, and should be compressed to the range of no more than 0.4 mm to 0.7 mm in the ocular environment.

The largest dimension of the particles should be at least 0.5 mm. The drainage system of the eye includes the punctum which is an opening or aperture on the radial aspect of both upper and lower eye lid margins (in the medial corner of the upper and lower eyelids). The punctum has an average diameter of 0.5 mm. The punctum provides an opening into the drainage ducts or the lacrimal canaliculi of the drainage system which provides drainage of material out of the eye area. Material leaves the canaliculi, and passes through the lacrimal sac and nasolacrimal duct. Thus, the largest dimension of the particles should be greater than the size of the punctum to hinder drainage of the particles out of the eye through the punctum. It should be noted that 0.5 mm is merely a minimum value of the greatest dimension, and according to certain preferred embodiments, the largest dimension is generally 1 to 2 mm, but can be 4 mm or even greater to maximize the amount of material delivered. In certain preferred embodiments the third dimension or width should be about 0.5 mm or greater which further helps prevent drainage of the particles through the punctum.

The balance of the two dimensions as discussed above provides a system which will not drain from the eye area, and which will at the same time reduce the chance of injury or irritation to the eye even though the system includes particles large enough such that drainage through the punctum is prevented. Thus, prolonged, continuous treatment is provided without irritation of the eye and without need for meticulous application requiring special insertion devices.

The particles can have any shape, including but not limited to: spheres, hemispheres, flat discs of any polygonal configuration, rounded discs, egg-shaped particles, cylinders, rods, elongated spaghetti-like forms, elongated box-forms, elongated ribbon forms, and others.

As discussed above, in certain preferred embodiments drug is dispersed throughout the particles. This dispersion of the drug can include placing the drug component in the fluid form of the bioerodible material prior to forming the film, mixing the drug throughout and then pouring the film

which is eventually cut into particles. According to other advantageous embodiments, the drug is added to the particles after cutting from the film. In these embodiments, the cut bioerodible particles are soaked in drug solution, and thereby absorb the drug. After the drug has been included in the bioerodible particles, the particles can then be suspended in the liquid medium.

It is contemplated that the amount of drug in the particles can be varied by soaking the particles in different concentrations of the drug. Further, different types of bioerodible material will absorb drug to varying extents. Thus, the amount of drug can be varied by using different types of bioerodible materials. Further, by varying the density of the particles, drug will be absorbed to different extents. For example, by increasing the particle material density, drug will be absorbed to a lesser degree than with a material less dense.

Figure 1, shows a form of the particles having bioerodible material 12 and drug 14 dispersed throughout according to certain preferred embodiments of the invention.

The drug can also be encapsulated inside an outer coating of the bioerodible material. Encapsulation can be achieved by casting. The drug can be added to the bioerodible material while it is in liquid or particle form and the mixture can be reduced to fine microcapsules by grinding or other methods. Alternatively, fine particles of the drug can be coated such as by suspending dry particles of the drug in an air stream and contacting that stream with a stream of bioerodible material that coats the material with a wall of bioerodible material.

Another suitable microencapsulation method is the co-ascervation technique. The co-ascervation technique includes formation of three immiscible phases, a liquid manufacturing phase, a core material phase and a liquid coating phase. Liquid coating is deposited on the core material and rigidized usually by thermal, cross-linking or desolvation.

Encapsulated particles 20 are shown in Figure 2, with a coating 12 of bioerodible material surrounding drug 14 according to certain preferred embodiments.

Once the particles are formed, they are then suspended in the liquid or ointment medium 16 (shown in Figures 1 and 2). The treatment system can include different types of particles having different drugs dispersed throughout. Further, the treatment system can include different types of bioerodible material in the particles such that a differentiated rate of erosion can be achieved, thus providing a time release system for continuous long-term release of material to the eye.

Although clearly not limited to the following

range, approximately 5 to 10 particles should be included in each dose. However, this dose can change depending upon the concentration of the drug, the type of drug, the treatment required for the specific patient, or for the specific condition. The particles in suspension can be included in a conventional eye dropper bottle which provides for simple self-administration. According to certain preferred embodiments, the particles are included in a single dose container. Thus, the entire dosage is included in a single container with a dispensing end which the patient opens and then drops the suspension into the eye. Thus, proper dosage is assured. As discussed above, the density of the liquid medium or the viscosity of the liquid medium can be used to assure uniform dispersion of the particles in the liquid medium or uniform dispersion can be provided by shaking immediately preceding administration.

In unique applications of the present invention, a liquid medium having drug dispersed throughout is used. Thus, the particles can include drug dispersed therein, as well as drug dispersed throughout the solution. Therefore, an additional high concentration of drug is delivered to the eye in the solution and a prolonged dosage is provided by the bioerodible particles. Further, it is contemplated to use particles having a drug dispersed therein different than the drug included in the solution. Thus, for different situations, drugs which are advantageously provided in a solution in a high dosage and which are not necessarily required over a period of time can be included in the solution and prolonged dosage of another drug can be provided in the particles. The carrier could include an element, for example aluronic acid, to increase the affinity of the carrier for the drug.

In certain preferred embodiments, particles are dispersed in a standard eye ointment vehicle. The ointment can then be administered to the eye using standard procedures. For example, the lower eyelid is lifted out while the patient is looking up, and the ointment is then applied in the conjunctival sac. The lids should be closed for about one minute to allow the ointment to melt.

According to other advantageous features, a specific bioerodible material could be used which absorbs drug in relation to the concentration of the drug in which it is suspended. Thus, a single type of bioerodible material particle could be put into different concentrations of drug and thus provide different dosages of drug depending on the concentration in which it was suspended. Such a bioerodible material is placed in a solution including drug, and equilibrium between the particles and the solution would determine the exact concentration and duration of action.

The following examples are offered by way of

illustration only and should not be construed as limiting the scope of the present invention in any way.

EXAMPLE I

A. A suspension of cross-linked collagen particles is prepared as follows:

Nine grams of collagen are added slowly with stirring to 40 grams of buffer solution at 90° C. The buffer solution includes one liter of distilled water, 7.1 grams of disodium hydrogen phosphate and 6.9 grams of sodium dihydrogen phosphate monohydrate. The pH should be 6.8. Forty ml of the phosphate buffer and 0.15 grams chlorobutanol are combined with the heating and stirring. Alternatively, the collagen can be added to the buffer solution after it is cooled to room temperature and the mixture is then heated to 90° C until the solution is complete.

The mixture is stirred thoroughly for four minutes until the temperature falls to 40° C and is then poured into a pan of polyvinylchloride to a thickness which will give a dry thickness in the range generally of about 0.5 mm to 0.7 mm. The resulting film is dried at room temperature for one day.

A solution of formaldehyde (1% by weight) is prepared by addition of 13.1 grams of 38 percent formaldehyde reagent to 487 grams phosphate buffer (pH 6.8). The collagen films are submerged in this buffered formaldehyde solution for 20 minutes at room temperature, quickly rinsed with water and soaked in ice water for 2 hours. The films are removed from the ice water and dried overnight.

The dried film is then cut into individual particles using a mold cutter. The mold cutter forms disc-shaped particles having a diameter of 1 mm, and a thickness of 0.4 mm which was the thickness of the dried film.

B. The particles are then placed in a solution of tobramycin at 25° C for 15 minutes. Concentration of drug in the solution is 40 mg per ml. The particles will absorb the drug solution.

The particles are then removed from the solution and allowed to dry for 2 hours.

A liquid medium made of sterile distilled water, 1%w. poly (vinyl alcohol) and 0.004% benzalkonium chloride is prepared.

A suspension of about 5 particles per 0.25 cc of carrier medium is prepared. The drops of the suspension can be administered from a dispenser 30 by dropping the suspension into the eye. Specifically, in certain embodiments, the lower eyelid 32 is pulled down and the suspension 34 is dropped into the area 36 between the eyelid 32 and the eye 38 as shown in Figure 3. One administration containing from about 3 to 6

particles will provide continuous delivery of tobramycin for about 6 hours.

EXAMPLE II

The particles for the suspension are prepared as described in Example IA. The particles are then suspended in a liquid medium made of sterile distilled water, 1%w poly (vinyl alcohol), 0.004% benzalkonium chloride and 0.1% dexamethasone. The suspension should be about 5 particles per 0.25 cc of carrier medium. The particles should be suspended for at least 20 minutes prior to administration.

The suspension described above is administered to the patient as described in Example IB.

EXAMPLE III

The particles for an ointment suspension are prepared as described in Example IA. The particles are then placed in a solution of garamycin at 25 °C for 20 minutes. Concentration of drug in the solution is 40 mg per milliliter. The particles will absorb the drug solution.

The particles including garamycin are then suspended in an ointment of petrolatum (40% solid petrolatum, 60% liquid petrolatum).

The ointment described above is administered to the patient using a tube with a wide dispenser opening.

EXAMPLE IV

The treatment suspension is prepared as described in Example IA except rather than pouring the liquid bioerodible mixture on a sheet of polyvinyl chloride, the mixture is poured into a mold. The mold forms particles in the shape of hemispheres (half spheres) having a thickness of about 0.4 mm and a diameter of about 1.0 mm.

EXAMPLE V

A. Nine grams of collagen are added slowly with stirring to 40 grams of buffer solution at 90 °C. The buffer solution includes one liter of distilled water, 7.1 grams of disodium hydrogen phosphate and 6.9 grams of sodium dihydrogen phosphate monohydrate. The pH should be 6.8. Forty ml of the phosphate buffer and 0.15 grams chlorobutanol are combined with the heating and stirring. Alternatively, the collagen can be added to the buffer solution after it is cooled to room temperature and the mixture is then heated to 90 °C until the solution is complete.

Three grams of cyclosporin are suspended in 5 ml of phosphate buffer. The resultant mixture is added immediately to the stirred collagen

solution as it cools to approximately 50 °C. The mixture is stirred thoroughly for four minutes until the temperature falls to 40 °C and is then poured onto a sheet of polyvinylchloride to a thickness which will dry to a thickness in the range of about 0.4 mm to 0.7 mm. The resulting film is dried at room temperature for one day.

A solution of formaldehyde (1% by weight) is prepared by addition of 13.1 grams of 38 percent formaldehyde reagent to 487 grams phosphate buffer (pH 6.8). The collagen films are submerged in this buffered formaldehyde solution for 20 minutes at room temperature, quickly rinsed with water and soaked in ice water for 2 hours. The films are removed from the ice water and dried overnight.

The dried film is then cut into individual particles using a mold cutter. The mold cutter forms disc-shaped particles having a diameter of 1 mm, and a thickness of 0.4 mm which was the thickness of the dried film.

B. The particles are then suspended in a liquid medium made of sterile distilled water, 1% w. poly(vinyl alcohol) and 0.004% benzalkonium chloride. A suspension of about 5 particles per 0.25 cc of carrier medium is prepared.

The suspension is then administered as described in Example IB.

EXAMPLE VI

A liquid carrier medium made of sterile distilled water, 1%w. poly (vinyl alcohol) and 0.004% benzalkonium chloride is prepared.

A suspension of about 5 collagen particles prepared as described in Example IA, per 0.25 cc of carrier medium is prepared. Also added to the carrier medium are about 5 globules of semi-solid petrolatum. These globules have three dimensions of about 0.5 mm by 1 mm by 1 mm. The drops of the suspension can be administered from a dispenser 30 by dropping the suspension into the eye. According to certain preferred embodiments, the lower eyelid 32 is pulled down and the suspension 34 is dropped into the area 36 between the eyelid 32 and the eye 38 as shown in Figure 3. One administration containing from about 3 to 6 particles will provide continuous delivery of the tear film components for about 6 hours.

EXAMPLE VII

The particles for an ointment suspension are prepared as described in Example IA. The particles are then placed in a liquid medium of sterile distilled water for 20 minutes. The particles will be hydrated and thus will incorporate the water therein.

The hydrated particles are then suspended in an ointment of petrolatum (40% solid petrolatum, 60% liquid petrolatum).

The ointment described above is administered to the patient using a tube with a wide dispenser opening.

EXAMPLE VIII

The treatment suspension is prepared as described in Example IA except rather than pouring the liquid bioerodible mixture on a sheet of polyvinyl chloride, the mixture is poured into a mold. The mold forms particles in the shape of hemispheres (half spheres) having a thickness of about 0.4 mm and a diameter of about 1 mm.

Although the present invention has been described and illustrated in detail, it is to be clearly understood that the same is by way of illustration and example only, and is not to be taken by way of limitation. The spirit and scope of the present invention are to be limited only by the terms of the appended claims.

Claims

1. An ophthalmic system comprising:
three-dimensional particles of bioerodible material being at least 0.5mm and in the range of 1 to 2mm in greatest dimension, being no greater than 0.4mm to 0.7mm in smallest dimension when disposed in an ocular environment, and
one of a liquid carrier and an ointment carrier having a pH acceptable to the eye in which the particles are suspended.
2. The system of claim 1 wherein the bioerodible material is at least one of collagen, gelatin, serum, polyvinyl alcohol, polymerized methycellulose or methycellulose derivatives.
3. The system of claim 1 or 2 wherein the particles have a smallest dimension no greater than 0.5mm in the suspension prior to administration.
4. The system of claim 1, 2 or 3 wherein the particles are in a soft, malleable form such that the particles are deformed by the eyelid when placed in the ocular environment between the eyelid and the eye and are comfortable if disposed between the eyelids.
5. The system of claim 4, wherein the particles are in a soft, semi-solid form.
6. The system of claim 4 or 5 wherein the particles are greater than about 0.4mm to 0.7mm in smallest dimension in the suspension prior to administration and are compressed to no more than 0.5mm in smallest dimension when disposed in the ocular environment between the eyelid and the eye.
7. The system of any of claims 1 to 6 wherein the particles are spherical, hemispherical, elongated cylindrical, cubical, rectangular, elongated rectangular or rounded disc-shaped in form.
8. The system of any of claims 1 to 7 wherein said greatest dimension is greater than 1mm.
9. The system of any of claims 1 to 8 wherein the particles conform to the undersurface of the eyelid after administration and are comfortable if disposed in between eyelids.
10. The system of any of claims 1 to 9 wherein the particles of bioerodible material are hydrated at the time of administration, thereby providing soft malleable particles.
11. An ophthalmic drug system according to any of claims 1 to 10, further comprising at least one ophthalmic drug included in the particles of bioerodible material.
12. The system of claim 11 wherein the ophthalmic drug is encapsulated in or dispersed throughout the particles of bioerodible material.
13. The system of claim 12 wherein the ophthalmic drug is encapsulated within a coating of the bioerodible material, with the ophthalmic drug released in the eye when the coating of bioerodible material erodes in response to the ocular environment.
14. The system of claim 12 wherein the ophthalmic drug is dispersed throughout the bioerodible material, with the ophthalmic drug continually released in the eye as said particles erode in response to the ocular environment.
15. An ophthalmic artificial tear system according to any of claims 1 to 10, comprising:
bioerodible mucin-type particles for releasing mucin-type material when placed in an ocular environment to provide a hydrophilic surface to hold aqueous material in the ocular environment;
lipid-type material for releasing lipid-type material when placed in the ocular environment to provide a layer to retard evaporation of

- aqueous material in the ocular environment;
aqueous-type material for releasing aqueous-type material when placed in the ocular environment;
wherein the mucin-type particles are suspended in at least one of the lipid-type material carrier and the aqueous-type material carrier.
16. An ophthalmic artificial tear system comprising bioerodable mucin-type particles for releasing mucin-type material when placed in an ocular environment to provide a hydrophilic surface to hold aqueous material in the ocular environment;
lipid-type material for releasing lipid-type material when placed in the ocular environment to provide a layer to retard evaporation of aqueous material in the ocular environment;
aqueous-type material for releasing aqueous-type material when placed in the ocular environment;
wherein the mucin-type particles are suspended in at least one of the lipid-type material carrier and the aqueous-type material carrier.
17. The system of claim 15 or 16 wherein the mucin-type particles are at least one of collagen, gelatin or serum.
18. The system of claim 15, 16 or 17 wherein at least a portion of the lipid-type material is in the form of particles.
19. The system of claim 18 wherein the lipid-type particles are at least one of petrolatum, fatty acids, fatty esters, waxes, fatty alcohols or lecithin.
20. The system of claim 18 wherein the lipid-type particles are at least one of glycoprotein, cholesterol or phospholipids.
21. The system of any of claims 1 to 20 wherein the mucin-type particles are in a malleable form.
22. The system of any of claims 18 to 21 wherein the mucin-type particles and the lipid-type particles have a greatest dimension of at least 0.5mm.
23. The system of claim 22 wherein the mucin-type particles and the lipid-type particles have a smallest dimension of no greater than about 0.4mm to 0.7mm when disposed in the ocular environment.
24. The system of any of claims 18 to 23 wherein the mucin-type particles and the lipid-type particles are suspended in an aqueous-type material carrier medium.
25. The system of claim 24 wherein a portion of the aqueous-type material is included in at least a portion of the mucin-type particles.
26. The system of claim 25 wherein the aqueous-type material is encapsulated in mucin-type particles.
27. The system of any of claims 18 to 26 wherein the mucin-type particles and the lipid-type particles are suspended in a lipid-type material carrier medium.
28. The system of claim 25 wherein the mucin-type particles having aqueous-type material included therein are suspended in a lipid-type material carrier medium.
29. The system of claim 28 further including an aqueous-type material carrier medium.
30. The system of claim 28 or 29 wherein the mucin-type particles are suspended in both a lipid-type material medium and an aqueous-type material medium.
31. The system of any of claims 15 to 30 wherein at least a portion of said lipid-type material is incorporated in said mucin-type particles.
32. The system of any of claims 15 to 31 wherein the carrier is a fluid carrier in which at least two of the mucin-type particles, the aqueous-type material and the lipid-type material are suspended.
33. The use of the system of any claims 1 to 32 for the preparation of an ophthalmic medication.

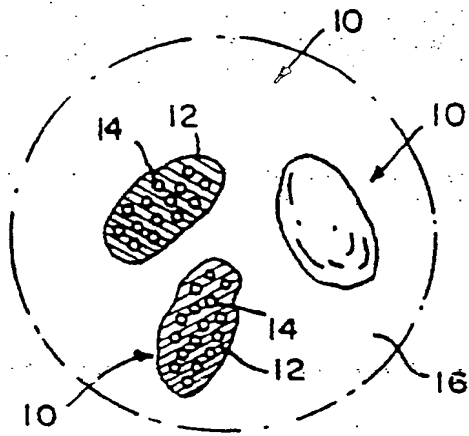


FIG. 1

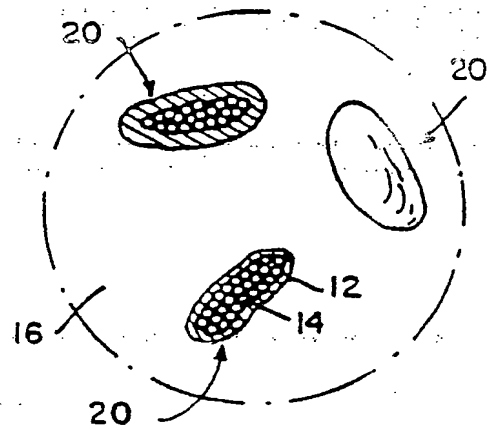


FIG. 2

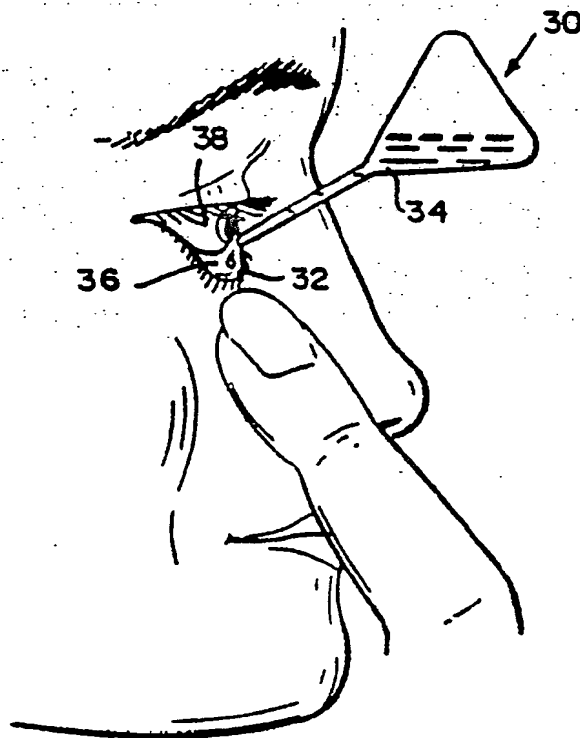


FIG. 3



European
Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 90 10 6084

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	US-A-4 865 846 (HERBERT E. KAUFMAN) * the whole document *	1-33	A 61 K 9/06 A 61 K 9/52
A,D	US-A-4 115 544 (JOHN W. SHELL) * the whole document *	1-33	
A	EP-A-0 251 680 (IOLAB,INC) * the whole document *	1-33	
A	EP-A-0 322 319 (VERNON G. WONG) * the whole document *	1-33	
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
			A 61 K
The present search report has been drawn up for all claims			
Place of search		Date of completion of search	Examiner
The Hague		09 November 90	SIATOU E
<div>CATEGORY OF CITED DOCUMENTS</div> <div>X : particularly relevant if taken alone</div> <div>Y : particularly relevant if combined with another document of the same category</div> <div>A : technological background</div> <div>D : non-written disclosure</div> <div>P : intermediate document</div> <div>T : theory or principle underlying the invention</div> <div>E : earlier patent document, but published on, or after the filing date</div> <div>D : document cited in the application</div> <div>L : document cited for other reasons</div> <div>& : member of the same patent family, corresponding document</div>			

THIS PAGE BLANK (USPTO)

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☒ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☒ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.

THIS PAGE BLANK (USPTO)